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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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David Grenville Holmes

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CORPORATE INTELLECTUAL PROPERTY  
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EXAMINER

ROYDS, LESLIE A

ART UNIT

PAPER NUMBER

1614

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/516,633	<b>Applicant(s)</b> HOLMES ET AL.	
	<b>Examiner</b> LESLIE A. ROYDS	<b>Art Unit</b> 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3-9,11-16 and 18-26 is/are pending in the application.
- 4a) Of the above claim(s) 3-5 and 14-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,6-9,11-13 and 18-26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>22 April 2009</u> .   | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

**Claims 1, 3-9, 11-16 and 18-26 are presented for examination.**

Applicant's Amendment and Information Disclosure Statement (IDS) filed April 22, 2009 has been received and entered into the present application.

Regarding the Information Disclosure Statement (IDS) filed April 22, 2009, the Examiner has not considered the cited reference. The information disclosure statement filed April 22, 2009 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because Applicant has failed to list any of the pertinent publication information, such as, e.g., a publication date, source of the publication, etc. of the reference to Baron et al. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claims 1, 3-9, 11-16 and 18-26 are pending. Claims 3-5 and 14-16 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 1, 6-9, 11-13 and 18-26 remain under examination. Claims 1 and 8 are amended. No claims are cancelled or newly added.

Applicant's arguments, filed April 22, 2009, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

#### ***Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

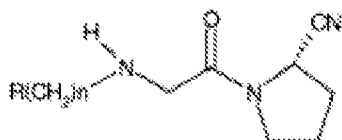
Claims 1 and 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, the preamble of instant claim 1 recites a “method of treating hyperlipidemia and or conditions associated with hyperlipidemia comprising administering to a mammal in need thereof”. The phrase “and or” in the preamble of the claim renders the scope of the claim indefinite because it is unclear if Applicant intends for the claim to circumscribe (1) treatment of hyperlipidemia *and* conditions associated with hyperlipidemia, (2) treatment of hyperlipidemia *or* conditions associated with hyperlipidemia, or (3) treatment of hyperlipidemia *and/or* conditions associated with hyperlipidemia. In other words, the conditions to be treated via the instantly claimed method are not clearly, precisely or deliberately set forth in the claims. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is necessary.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 1, 6-9, 11-13 and 18-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 1 recites the administration of a compound of formula (I), which has the chemical



structure

, and defines R as a substituted adamantyl group and N as 0 to 3,

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wherein the compound may be either in free form or in acid addition salt form. However, Applicant has failed to define the identity of "n" in the above formula. The claim as presently written fails to provide any indication of what values of "n" are permitted in the claimed formula. Furthermore, Applicant defines "N" as 0-3, but it is unclear how "N" in the above chemical formula can be defined as 0-3, since it appears that "N" as presented in the generic formula is intended to circumscribe a nitrogen atom. As a result of this ambiguity in the claim, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is necessary.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination, Applicant's "n" group will be understood to be defined as 0-3, and "N" is understood to circumscribe a nitrogen atom.

***Claim Rejections - 35 USC § 103 (New Grounds of Rejection)***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

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to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-9, 11-13 and 18-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Villhauer (U.S. Patent No. 6,166,063; 2000) in view of Luskey et al. (U.S. Patent No. 6,262,118; 2001).

Villhauer teaches the instantly claimed compound of formula (IC) and pharmaceutical compositions thereof (abstract; col.1, 1.19-31; Example 1), wherein the acid addition salt forms of the compound may also be used (col.1, 1.19-31), which function as a dipeptidyl peptidase-IV (DPP-IV) inhibitors (col.4, 1.30-32) and is disclosed for use in a method for treating conditions mediated by DPP-IV, comprising administering to a mammal in need of such treatment a therapeutically effective amount of the disclosed compound(s) or pharmaceutically acceptable acid addition salts thereof (col.4, 1.19-24), wherein the condition mediated by DPP-IV includes, *inter alia*, non-insulin-dependent diabetes, arthritis, obesity, osteoporosis, and other conditions related to impaired glucose tolerance (abstract).

Villhauer et al. fails to specifically teach the treatment of patients in need of treatment of hyperlipidemia and/or atherosclerosis (claims 1 and 8); the concomitant use of another active agent (claims 8, 12, 21, 23 and 25); or the concomitant use of another active agent for the purpose of lowering LDL, Lp(a) and/or VLDL (claims 9, 19-20, 22, 24 and 26).

Luskey et al. teaches that the premature development of atherosclerosis and hyperlipidemia are characteristic features of patients with diabetes and that, specifically, hyperlipidemia is a precipitating factor for this disease (col.2, 1.1-8). Luskey et al. further teaches an effective combination therapy for modulating the symptoms of atherosclerosis, wherein one or more of the following active agents may be used: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also

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known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as  $\beta$ -sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrozil; vitamin B<sub>6</sub> (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B<sub>12</sub> (also known as cyanocobalamin); vitamin B<sub>3</sub> (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and  $\beta$ -carotene; a  $\beta$ -blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin (col.17, 1.26-50).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the disclosed DPP-IV inhibitor of formula (IC) of Villhauer for the treatment of diabetes would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of atherosclerosis in a patient in need of such treatment because: (1) the compound of Villhauer was known to have efficacy in treating patients that suffer from diabetes *per se* and (2) patients that have diabetes also suffer from premature development of atherosclerosis and hyperlipidemia that precipitate the development of diabetes, as evidenced by Luskey et al. Villhauer provides the clear teaching that the instantly claimed compound of Formula (IC) is, in fact, effective for treating all diabetes patients, i.e., 100% of patients with diabetes, without exclusion. Of this entire population of diabetes patients, Luskey et al. provides the factual extrinsic evidence demonstrating that a subpopulation of diabetes patients also suffers concomitantly from atherosclerosis and/or hyperlipidemia. Accordingly, the suggestion of Villhauer to use the claimed compound of Formula (IC) for treating any diabetes patient is a clear suggestion to use it in any subpopulation of diabetes patients, such as those

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patients also suffering from concomitant atherosclerosis and/or hyperlipidemia, with the reasonable expectation of the same (or at least substantially equivalent) level of efficacy in treating this subpopulation of patients with atherosclerosis and/or hyperlipidemia as would be expected in the treatment of diabetes patients *per se*. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same host, whatever effect(s) the instantly claimed compound of Formula (IC) has in treating atherosclerosis and/or hyperlipidemia (including the instantly claimed effects recited in instant claim 9 regarding the lowering of LDL levels, Lp(a) and/or VLDL levels) must necessarily be present in the method disclosed by Villhauer, absent factual evidence to the contrary. See MPEP §2112.

Further, regarding the concomitant use of an antihyperlipidemic agent, plasma HDL-raising agent, etc. as presently claimed (claims 8-9, 12 and 19-26), Luskey et al. teaches a multitude of agents that may be used in combination therapies for the treatment of atherosclerosis and the symptoms and complications thereof, including an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), etc. (col.17, l.26-50).

One of ordinary skill in the art would have been motivated to combine the pharmaceutical composition of Villhauer, which comprises the compound of Formula (IC), with the combination therapies as taught by Luskey et al. because Luskey et al. provides a clear teaching that a subpopulation of diabetes patients also suffers concomitantly from atherosclerosis and/or hyperlipidemia and further provides a clear teaching of the efficacy of such combination therapies for treating atherosclerosis and/or hyperlipidemia. In view of such teachings, the use of a multivalent therapy comprising an effective anti-atherosclerosis and/or anti-hyperlipidemic agent [e.g., in this case, an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g.,



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an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), etc.] in combination with an effective diabetes-treating agent would have been *prima facie* obvious to one of ordinary skill in the art treating patients suffering from diabetes. Such a person would have been motivated to do so not only to provide the diabetic patient with an effective diabetes-ameliorating pharmaceutical agent (i.e., the compound of Formula (IC)), but also to provide this particular subpopulation of diabetics that concomitantly suffer from atherosclerosis and/or hyperlipidemia an effective pharmacologic means of treating such conditions via using known anti-atherosclerotic and/or anti-hyperlipidemic agents, such as the agents disclosed by Luskey et al. This is because it is generally *prima facie* obvious to use, in combination, two or more agents to treat multiple symptoms resulting from the same condition in order to provide a means of ameliorating the medical condition that triggered such symptoms, and further thereby improving the patient's overall health.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-9, 11-13 and 18-26 remain provisionally rejected over claims 6 and 9 of copending U.S. Patent Application No. 11/815,536; or claim 6 of copending U.S. Patent Application No. 11/868,129; or claim 8 of copending U.S. Patent Application No. 11/497,130, each already of record, for the reasons of record set forth at p.5-9 of the previous Office Action dated December 3, 2008, of which

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said reasons are hereby incorporated by reference.

Applicant requests that the rejections be held in abeyance until claims are allowed in one or more of the cited applications.

In view of the fact that none of the claims in the copending applications have been allowed, and further in view of the fact that Applicant has failed to provide a Terminal Disclaimer and/or remarks directed to the rejections set forth *supra*, the rejections remain proper and are maintained.

### ***Double Patenting (New Grounds of Rejection)***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-9, 11-13 and 18-26 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 7, 10-12 and 18 of U.S. Patent Application No. 10/579,580 in view of Luskey et al. (U.S. Patent No. 6,262,118; 2001).

For the purposes of the instant rejection(s), please note that Applicant defines the compound of Formula (IC) as being synonymous with the chemical name pyrrolidine, 1-[3-hydroxy-1-(adamantyl)amino] acetyl-2-cyano, (S), as stated at p.4 of the instant specification.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

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Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending applications are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims are directed to a method for treating, *inter alia*, hyperlipidemia or atherosclerosis, comprising administering to a warm-blooded animal, including man, in need thereof a jointly effective amount of a DPP-IV inhibitor or a pharmaceutically acceptable salt thereof and at least one therapeutic agent selected from an anti-obesity agent or pharmaceutically acceptable salt thereof, an appetite regulating agent or a pharmaceutically acceptable salt thereof and a renin inhibitor or a pharmaceutically acceptable salt thereof, wherein the DPP-IV inhibitor is selected from, *inter alia*, (S)-1-[(3-hydroxy-1-adamantyl)amino] acetyl-2-cyano-pyrrolidine.

The copending claims fail to teach the use of a concomitant agent, such as an antihyperlipidemic agent, plasma HDL-raising agent, etc. as presently claimed (claims 8-9, 12 and 19-26).

Luskey et al. further teaches an effective combination therapy for modulating the symptoms of atherosclerosis, wherein one or more of the following active agents may be used: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as  $\beta$ -sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrozil; vitamin B<sub>6</sub> (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B<sub>12</sub> (also

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known as cyanocobalamin); vitamin B<sub>3</sub> (also known as nicotinic acid and niacinamide, *supra*); anti-oxidant vitamins, such as vitamin C and E and  $\beta$ -carotene; a  $\beta$ -blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin (col.17, 1.26-50).

One of skill in the art would have also found it *prima facie* obvious to combine the formulation of the copending claims with those combination therapies disclosed by Luskey et al. because Luskey et al. teaches the efficacy of these combination therapies for the treatment of atherosclerosis and the symptoms associated therewith. Motivation to administer both compounds/compositions together flows logically from the very fact that each discrete agent was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two agents, when combined, would have, at minimum, additive, if not synergistic, anti-atherosclerotic and/or anti-hyperlipidemic effects when combined. As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

Accordingly, provisional rejection of claims 1, 6-9, 11-13 and 18-26 is proper over claims 7, 10-12 and 18 of U.S. Patent Application No. 10/579,580, as claiming obvious and unpatentable variants thereof.

Claims 1, 6-9, 11-13 and 18-26 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-6, 8 and 16 of U.S. Patent Application No. 11/576,860; or claims 9, 12-19 and 20-26 of U.S. Patent Application No. 11/577,941; or claims 1, 16-18 and 34 of U.S. Patent Application No. 11/628,546; or claims 5-7, 13-14 and 18 of U.S.

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Patent Application No. 12/067,822, each alternatively in view of Luskey et al. (U.S. Patent No. 6,262,118; 2001), and citing to STN Registry No. 274901-16-5 as evidence.

For the purposes of the instant rejection(s), please note that:

(1) Applicant defines the compound of Formula (IC) as being synonymous with the chemical name pyrrolidine, 1-[3-hydroxy-1-adamantyl]amino] acetyl-2-cyano, (S), as stated at p.4 of the instant specification; and

(2) STN Registry No. 274901-16-5 is cited to show that the compound identified as Formula (IC) is also synonymous with the chemical name vildagliptin by virtue of their shared registry number and identical chemical structure.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending applications are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims of the '860 application clearly provide for a method for the treatment of diseases and disorders that may be inhibited by DPP-IV inhibition and/or by inhibiting the PDGF tyrosine kinase inhibitor comprising administering to a warm-blooded animal in need thereof a jointly effective amount of a DPP-IV inhibitor or salt thereof with at least one PDGE receptor tyrosine kinase inhibitor and at least one additional pharmaceutically acceptable carrier, wherein the disease is, *inter alia*, diabetes mellitus, and the DPP-IV inhibitor is provided for in copending claim 16 and is (S)-1-[(3-hydroxy-1-adamantyl)-amino] acetyl-2-cyano-pyrrolidine.

The copending claims of the '941 application clearly provide for a method for treating a condition

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mediated by DPP-IV comprising administering to a warm-blooded animal in need thereof a jointly therapeutically effective amount of (S)-1-[(3-hydroxy-1-adamantyl) amino]acetyl-2-cyano-pyrrolidine or a salt thereof in combination with metformin or a salt thereof and pioglitazone or rosiglitazone or salts thereof. Note that the copending specification defines the phrase "conditions mediated by DPP-IV" at p.24 as, *inter alia*, diabetes. In the instant case, the copending specification is being relied upon solely to define the term "conditions mediated by DPP-IV", which is consistent with the MPEP at §804, which states, "The specification can be used as a dictionary to learn the meaning of a term used in the patent claim. *Toro Co. v. White Consol. Indus., Inc.* 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999)."

The copending claims of the '546 application clearly provide for the treatment of type 2 diabetes comprising administering daily a therapeutically effective amount of metformin or a pharmaceutically acceptable salt thereof in combination with 50 mg of (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine or a pharmaceutically acceptable salt thereof to a patient in need thereof.

The copending claims of the '822 application clearly provide for a method for the treatment of diseases and disorders that may be inhibited by DPP-IV inhibition, comprising administering to a warm-blooded animal, including man, in need thereof, a jointly effective amount of a combination of a DPP-IV inhibitor or a pharmaceutically acceptable salt thereof with at least one active ingredient selected from an immunosuppressive or immunomodulator agent or a pharmaceutically acceptable salt thereof and at least one additional pharmaceutically acceptable carrier, wherein the condition may be, *inter alia*, diabetes. Note that the copending specification defines DPP-IV inhibitors at p.8 as, *inter alia*, the compound 1-[(3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine. Again, in the instant case, the copending specification is being relied upon solely to define the term "DPP-IV inhibitor", which is consistent with the teachings of the MPEP at §804. See *Toro Co. v. White Consol. Indus., Inc.* (citation already provided).

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The copending claims fail to specifically teach the treatment of patients in need of treatment of hyperlipidemia and/or atherosclerosis (claims 1 and 8); the concomitant use of another active agent (claims 8, 12, 21, 23 and 25); or the concomitant use of another active agent for the purpose of lowering LDL, Lp(a) and/or VLDL (claims 9, 19-20, 22, 24 and 26).

Luskey et al. teaches that the premature development of atherosclerosis and hyperlipidemia are characteristic features of patients with diabetes and that, specifically, hyperlipidemia is a precipitating factor for this disease (col.2, l.1-8). Luskey et al. further teaches an effective combination therapy for modulating the symptoms of atherosclerosis, wherein one or more of the following active agents may be used: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as  $\beta$ -sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrozil; vitamin B<sub>6</sub> (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B<sub>12</sub> (also known as cyanocobalamin); vitamin B<sub>3</sub> (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and  $\beta$ -carotene; a  $\beta$ -blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin (col.17, l.26-50).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the

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art at the time of the invention that the DPP-IV inhibitor of the copending claims used for the treatment of diabetes would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of atherosclerosis in a patient in need of such treatment because: (1) the copending compound was taught to have efficacy in treating patients that suffer from diabetes *per se* and (2) patients that have diabetes also suffer from premature development of atherosclerosis and hyperlipidemia that precipitate the development of diabetes, as evidenced by Luskey et al. The copending claims provide the clear teaching that the instantly claimed compound of Formula (IC) (synonymous with pyrrolidine, 1-[3-hydroxy-1-adamantyl)amino] acetyl-2-cyano, (S) or vildagliptin as recited in the copending claims) is, in fact, effective for treating all diabetes patients, i.e., 100% of patients with diabetes, without exclusion. Of this entire population of diabetes patients, Luskey et al. provides the factual extrinsic evidence demonstrating that a subpopulation of diabetes patients also suffers concomitantly from atherosclerosis and/or hyperlipidemia. Accordingly, the teaching of the copending claims to use the claimed compound of Formula (IC) for treating any diabetes patient is a clear suggestion to use it in any subpopulation of diabetes patients, such as those patients also suffering from concomitant atherosclerosis and/or hyperlipidemia, with the reasonable expectation of the same (or at least substantially equivalent) level of efficacy in treating this subpopulation of patients with atherosclerosis and/or hyperlipidemia as would be expected in the treatment of diabetes patients *per se*. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same host, whatever effect(s) the instantly claimed compound has in treating atherosclerosis and/or hyperlipidemia (including the instantly claimed effects recited in instant claim 9 regarding the lowering of LDL levels, Lp(a) and/or VLDL levels) must necessarily be present in the methods of the copending claims, absent factual evidence to the contrary. See MPEP §2112.

Further, regarding the concomitant use of an antihyperlipidemic agent, plasma HDL-raising agent, etc. as presently claimed (claims 8-9, 12 and 19-26), Luskey et al. teaches a multitude of agents



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that may be used in combination therapies for the treatment of atherosclerosis and the symptoms and complications thereof, including an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), etc. (col.17, 1.26-50).

One of ordinary skill in the art would have been motivated to combine the pharmaceutical compositions of the copending claims, which comprises the instantly claimed compound of Formula (IC), with the combination therapies as taught by Luskey et al. because Luskey et al. provides a clear teaching that a subpopulation of diabetes patients also suffers concomitantly from atherosclerosis and/or hyperlipidemia and further provides a clear teaching of the efficacy of such combination therapies for treating atherosclerosis and/or hyperlipidemia. In view of such teachings, the use of a multivalent therapy comprising an effective anti-atherosclerosis and/or anti-hyperlipidemic agent [e.g., in this case, an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), etc.] in combination with an effective diabetes-treating agent would have been *prima facie* obvious to one of ordinary skill in the art treating patients suffering from diabetes. Such a person would have been motivated to do so not only to provide the diabetic patient with an effective diabetes-ameliorating pharmaceutical agent (i.e., the compound of Formula (IC)), but also to provide this particular subpopulation of diabetics that concomitantly suffer from atherosclerosis and/or hyperlipidemia an effective pharmacologic means of treating such conditions via using known anti-atherosclerotic and/or anti-hyperlipidemic agents, such as the agents disclosed by Luskey et al. This is because it is generally *prima facie* obvious to use, in combination, two or more agents to treat multiple symptoms resulting from the same condition in order to provide a means of ameliorating the medical condition that triggered such

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symptoms, and further thereby improving the patient' s overall health.

Accordingly, provisional rejection of claims 1, 6-9, 11-13 and 18-26 is proper over claims 5-6, 8 and 16 of U.S. Patent Application No. 11/576,860; or claims 9, 12-19 and 20-26 of U.S. Patent Application No. 11/577,941; or claims 1, 16-18 and 34 of U.S. Patent Application No. 11/628,546; or claims 5-7, 13-14 and 18 of U.S. Patent Application No. 12/067,822, as claiming obvious and unpatentable variants thereof.

### ***Conclusion***

Rejection of claims 1, 6-9, 11-13 and 18-26 is proper.

Claims 3-5 and 14-16 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Leslie A. Royds/

Patent Examiner, Art Unit 1614

August 27, 2009

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614